BIODEGRADABLE POLYMERS AS DRUG CARRIERS

Peter Markland
Southern Research Institute, Birmingham, Alabama, U.S.A.

Victor C. Yang
The University of Michigan, Ann Arbor, Michigan, U.S.A.

OVERVIEW

Polymers first developed in the search for biodegradable suture materials have proven to be useful and successful for long-term drug delivery applications. Biodegradable polymers are highly desirable in these situations because they degrade in the body to biologically inert and compatible molecules. By incorporating drug into biodegradable polymers, dosage forms that release the drug over a prolonged length of time can be prepared in a variety of shapes and sizes. No secondary surgical procedures are needed after completion of the dosing regimen since the remaining polymer dosage form will be degraded and cleared by the body. As a result, biodegradable polymers offer a novel approach for developing sustained release drug delivery systems that are simple and convenient to the patient.

Many different biodegradable polymer chemistries have been proposed for these applications; however, the most common and successful are the polyesters that were first investigated as degradable sutures. These polymers include poly(glycolide), poly(D,L-lactide), and their related copolymers poly(D,L-lactide-co-glycolide). Many commercial products based on these materials are currently on the market, including Decapeptyl®, Lupron Depot®, and Sandostatin LAR®. In traditional parenteral depot applications, biodegradable polymers have been used simply as inert carrier vehicles. Preparation of the dosage form was carried out, by various means, by simply incorporating the drug into the polymer matrix. However, the effective delivery of new drug therapies, including peptides, proteins, and genetic- and cell-based drugs, places greater demands on the performance of the polymer platform. Consequently, new polymer chemistries and novel dosage form design are being investigated in attempts to produce tailor-made dosage forms that are capable of enhancing the delivery and efficacy of these drugs.

INTRODUCTION

A wide variety of delivery systems have been developed for the purpose of prolonging the release and, ultimately, bioavailability of drugs to the body. Examples include the transdermal patch, oral dosage forms such as osmotic pumps and swellable hydrophilic polymer matrices, and various types of polymer-based parenteral depot formulations (1, 2). Depot sustained release formulations can overcome limitations associated with oral or transdermal administration routes. Several of these limitations include poor drug stability in the GI tract, low drug permeability through the GI mucosa or stratum cornea, rapid clearance from first-pass metabolism, and the need for delivery for more than a few days. Many interesting and successful parenteral depot systems for sustained release applications have been developed. Such systems can be distinguished into degradable and nondegradable delivery systems based on the properties of the polymers.

One example of a nondegradable delivery system is Norplant® (Wyeth-Ayerst) which has been shown successful in prevention of pregnancy for up to five years (3). This delivery system consists of six small, closed tubes made of a silicone rubber copolymer of dimethylsiloxane and methylvinylsiloxane (Silastic®) and is implanted subcutaneously by scalpel incision or via trocar. Each tube contains 36 mg of the progestin hormone levonorgestrel. At termination of the dosing regimen, a nondegradable delivery system like this requires a secondary surgical procedure to retrieve the implanted device from the body. Such a retrieval procedure can be undesirable for several reasons including the added cost, the possibility of complications during retrieval, the risk of infection, and the lack of patient compliance. Although Norplant® is widely considered a safe and highly cost-effective method of contraception (4), there nevertheless has been a precipitous drop in demand for this product in

the United States since 1994. This decrease in interest has been attributed, in large part, to the difficulties associated with removal of the implanted rods along with the publicity created by these clinical problems (5).

Consequently, polymers that can degrade into biologically compatible components under physiologic conditions present a far more attractive alternative for the preparation of drug delivery systems. The use of biodegradable polymers precludes the need for retrieval at the conclusion of the dosing regimen, thereby avoiding the potential complications associated with the use of nondegradable systems. Degradation may take place by a variety of mechanisms, although it generally relies on either erosion or chemical changes to the polymer. Degradation by erosion normally takes place in devices that are prepared from soluble polymers. In such instances, the device erodes as water is absorbed into the system causing the polymer chains to hydrate, swell, disentangle, and, ultimately, dissolve away from the dosage form. Alternatively, degradation could result from chemical changes to the polymer including, for example, cleavage of covalent bonds or ionization/protonation either along the polymer backbone or on pendant side-chains. A number of degradation schemes have been described that characterize how chemical degradation of the polymer or of polymer–drug conjugates can be utilized to achieve drug release (6, 7).

The most widely studied biodegradable polymers include those which undergo chemical degradation through random hydrolysis of the covalent bonds constituting the backbone of the polymer chains. Random chain scission results in a reduction in the molecular weight of the polymer. As this process continues over time, polymer chains become progressively shorter resulting, at some point in time, in the loss of mechanical integrity in the dosage form. Ultimately, the degradation process proceeds until polymer fragments are degraded to soluble oligomers or individual monomers. As a necessity due to this process, biodegradable polymers and their degradation products must be biologically compatible and nontoxic. Consequently, the monomers typically used in the preparation of biodegradable polymers are often molecules that are endogenous to biological systems. The most common class of biodegradable polymers is the hydrolytically labile polyesters prepared from lactic acid, glycolic acid, or combinations of these two molecules. Polymers prepared from these individual monomers include poly(D,L-lactide) (PLA), poly(glycolide) (PGA), and the copolymer poly(D,L-lactide-co-glycolide) (PLG).

The distinctions between chemical and erosion degradation mechanisms, however, are by no means absolute, and there are instances where both processes contribute to the overall degradation and resorption of a drug delivery system. For instance, copolymers of glutamic acid and ethyl glutamic acid have been studied for the release of the narcotic antagonist naltrexone (8). In this case, hydrolysis of the ethyl ester side-chain converts this copolymer to the soluble polymer poly(glutamic acid). Following hydrolysis, the polymer device erodes as the soluble polymer chains dissolve away from the device. In addition, there are many other examples where both chemical degradation and physical erosion are involved in the final disintegration and resorption of the dosage form. In this regard, the terms such as "biodegradable" and "bioerodible" are sometimes used interchangeably in the literature while, at other times, they can be used to refer to distinct degradation processes. Consequently, care should be taken when reviewing the literature to interpret how these terms are being used. In some cases, the term "biodegradation" is limited to the description of chemical processes (chemical changes that alter either the molecular weight or solubility of the polymer) while "bioerosion" may be restricted to refer to physical processes that result in weight loss of a polymer device.

HISTORY

The use of biodegradable polymers in drug delivery applications grew from the search for polymers that could be employed as degradable sutures. Synthetic polymers such as poly(glycolic acid) were first developed in the 1950s (9); however, their poor hydrolytic stability made them unsuitable for permanent applications. This attribute, however, made these materials useful for applications such as sutures that could benefit from their ability to degrade in the presence of moisture (10, 11). Examples include Dexon® and Vicryl® sutures prepared from poly(glycolic acid) and poly(lactide-co-glycolide), respectively (10, 12). The utility of these materials as degradable sutures further led to their application in the development of sustained release drug delivery formulations. In 1970, Yolles et al. reported the use of the poly(lactic acid) biodegradable system for delivery of the narcotic antagonist cyclazocine (13). At about the same time, a number of other drugs including anticancer agents (14), steroids (15), and other narcotic antagonists (16–18) were reported to be delivered from biodegradable formulations. Many reviews catalog the early development of this technology for the sustained delivery of a variety of small molecule drugs (19–21).

More recently, the growth of biotechnology has led to the identification of many potent and powerful protein- and

gene-based macromolecular drugs. However, delivery of these drugs to the body in an efficacious manner without sacrificing the quality of life of the patient continues to be a major obstacle. Gastric proteases and low permeability across the gastrointestinal epithelium mean that macromolecular drugs have poor bioavailability via the oral route. Instead, these drugs are normally dosed by injection (e.g., subcutaneous, intramuscular, or intravenous). However, the short biological half-lives of these molecules requires that frequent parenteral injections be performed in order to maintain treatment efficacy. Despite the obvious need to develop long-term delivery systems for these highly valuable drugs, the application of this technology has been fraught with obstacles (22–24). Polymer–drug interactions, processing conditions, and the internal pH, temperature, and moisture levels within the implanted device have contributed to difficulties retaining drug stability before being released from the implanted device.

In spite of these complications, considerable achievements have been made in the development of biodegradable delivery systems for proteins and, in particular, bioactive peptides. Most of the commercial success over the past decade has been achieved using the polyester PLA and the various copolymers of PLG. In particular, a number of biodegradable delivery systems have been developed for synthetic analogs of luteinizing hormone-releasing hormone (LHRH). Sanders et al., for instance, demonstrated the release of nafarelin acetate for over 30 days from microsphere formulations of PLG with a 50:50 molar ratio of the lactide and glycolide monomers (50:50 PLG) (25). The first such system to the market was Decapeptyl® (Ipsen Biotech), a microsphere depot formulation for treatment of prostate cancer (Fig. 1) (26). This product delivers 3.75 mg of an LHRH analog over a 30-day period. More recently, TAP Pharmaceuticals (Deerfield, IL) commercialized a series of depot microsphere formulations of the LHRH analog leuprolide acetate under the trade name Lupron Depot®. Products prepared from either PLG or PLA are presently available that can provide peptide release over 1, 3, and 4 months (3). Lupron Depot® formulations are indicated for the treatment of endometriosis (27), prostate cancer (28), and precocious puberty in children (29).

In contrast to these microsphere formulations, Zoladex® (AstraZeneca) is a small implantable cylinder (approximately 1 mm in diameter and 10 mm in length) containing goserelin acetate in a polymer matrix of 50:50 PLG. This system delivers approximately 3.6 mg drug over a 1-month period and is indicated for the treatment of prostate cancer. A second Zoladex® system containing 10.6 mg goserelin has also been developed to release the drug for over 3 months (3).

The synthetic somatotropin analog octreotide acetate has been successfully formulated into a microsphere formulation composed of PLG. This product, Sandostatin LAR® (Novartis), has been used for acromegaly treatment (30) as well as the treatment of diarrhea and flushing episodes associated with metastatic carcinoid (31).

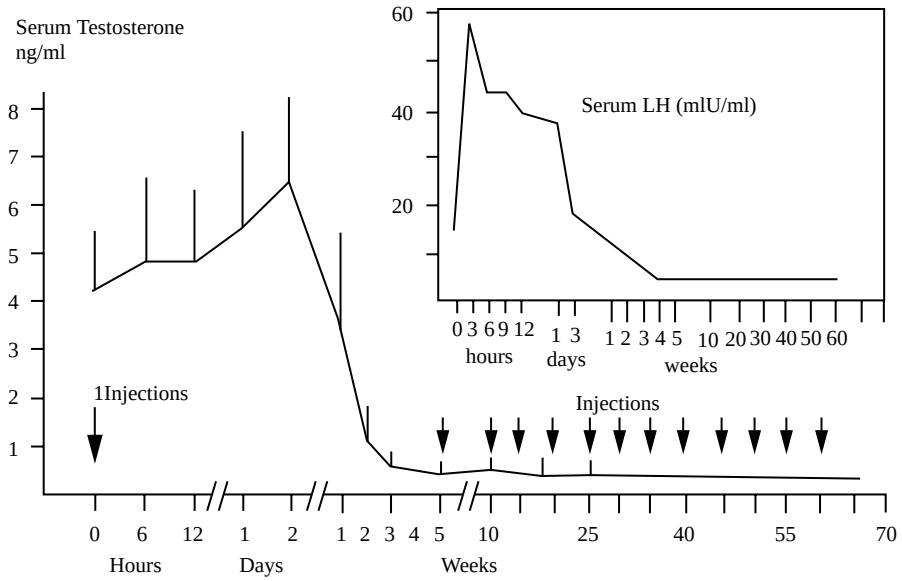


Fig. 1 Serum LH and testosterone concentrations of 22 human subjects treated at 5 week intervals with the biodegradable depot formulation Decapeptyl (3 mg LHRH per dose). (From Ref. 26.)

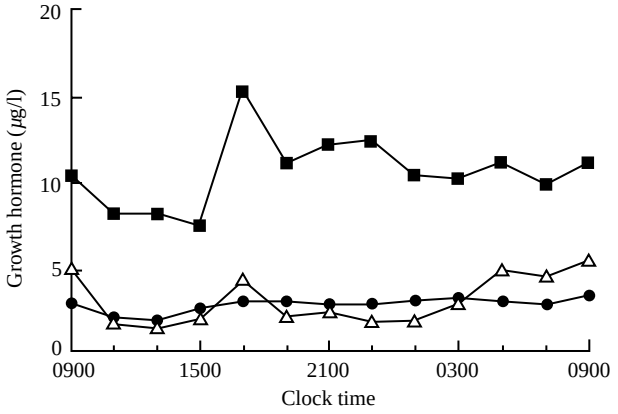


Fig. 2 The influence of Sandostatin LAR biodegradable depot formulation on the mean plasma growth hormone concentrations in humans. Plasma concentrations are shown over a 24 hour period 28 days after administration of a second monthly 20 mg dose of Sandostatin LAR, ●. For comparison, plasma concentrations are provided for untreated controls, ■, and for patients receiving multiple daily subcutaneous octreotide injections, Δ. (From Ref. 30.)

The depot formulation, given once monthly, is reported to be as well tolerated and effective as octreotide solutions that require long-term subcutaneous dosing 2–3 times daily (Fig. 2). This example clearly illustrates the potential for biodegradable sustained release formulations to significantly improve quality of life.

In December 1999, the first protein biodegradable depot formulation received regulatory approval. Nutropin-Depot® (Genentech) contains somatotropin, a recombinant human growth hormone (rhGH) having a molecular weight of 22,125 D, within PLG microspheres. Protein activity was preserved by preparing the microspheres from an insoluble zinc–hormone complex (Fig. 3) (32).

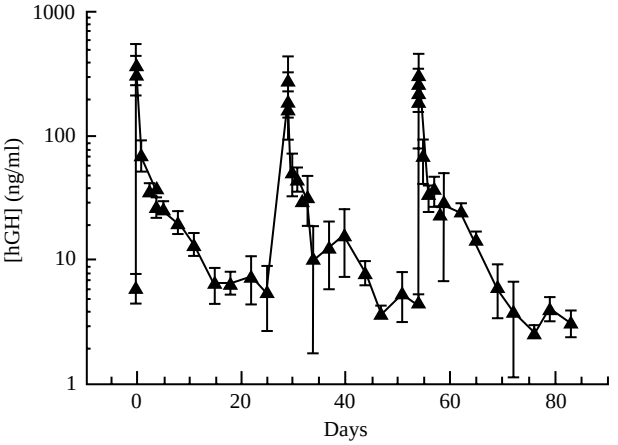


Fig. 3 Serum human growth hormone (hGH) levels in immunosupressed rats receiving three monthly doses of a biodegradable depot formulation containing 7.5 mg rhGH. (From Ref. 32.)

While many different polymer chemistries have been developed for drug delivery applications, only one class of polymer beside the polyesters has received regulatory approval. Gliadel® is a thin wafer containing the chemotherapeutic agent carmustine (BCNU) in a polyanhydride polymer matrix. Gliadel® received conditional approval in 1996 as an adjunct therapy following surgical removal of recurrent glioblastoma multiforme (GBM) tumors (3).

Obviously, the regulatory status of polyesters means that these materials dominate the field as far as commercial development is concerned. However, there is a myriad assortment of polymers that continue to be developed for drug delivery applications. These efforts are aimed at developing new polymeric materials designed specifically to overcome obstacles in drug delivery, bioavailability, or stability. Additionally, new engineering or processing techniques are also being developed to aid the design of novel dosage forms that can enhance drug delivery characteristics and the use of these polymeric materials in a variety of new biomedical applications.

FACTORS AFFECTING POLYMER SELECTION

Both synthetic polymers and those derived from naturally occurring sources have been evaluated in biodegradable drug delivery applications. Examples of several classes of biodegradable polymers are presented in Table 1. There are a variety of polymer properties or attributes to be considered when selecting a biodegradable polymer. Many of these are listed in Table 2. One of the most critical considerations is the regulatory requirement for a particular application. If an application requires rapid development and commercialization, then the polymer selection will most likely be made from among those polyesters that have already received regulatory approval. Another factor to consider is whether to use homopolymers consisting of a single monomeric repeat unit or copolymers containing multiple monomer species. If copolymers are to be employed, then the relative ratio of the different monomers may be manipulated to change polymer properties. It should be noted that polymer composition would directly dictate many of the polymer physicochemical properties listed in Table 2 including bulk hydrophilicity, morphology, structure, and the extent of drug–polymer interactions (e.g., drug solubility in the

Table 1 Common classes and examples of biodegradable polymers

Type	Class	Examples
Synthetic polymers	Polyamide	Polyamino acids, Polypeptides
	Polyester	Poly(glycolide)
		Poly(D,L-lactide)
		Poly(D,L-lactide-co-glycolide)
		Poly(ϵ-caprolactone)
		Poly(dioxanone)
		Poly(hydroxybutyrate)
	Polyanhydride	
	Polyorthoester	
	Polyphosphazene	
	Polyphosphoester	Polyphosphate
		Polyphosphonate
		Polyphosphite
Naturally occurring polymers	Polysaccharides	Dextran
		Chitosan
		Alginate
		Starch
		Hyaluronic acid
	Polypeptides, Proteins	Collagen
		Gelatin
		Bovine serum albumin (BSA)
		Human serum albumin (HSA)

polymer). Ultimately, these properties will all influence the performance of the drug delivery system via changes to the relative rates of mass transport (e.g., water in and solute or drug out of the system) and the degradation rate of both the polymer and the device.

In addition to polymer composition, the thermal attributes of the polymer, as described by the glass transition temperature (T_g) and melting temperature (T_m), can also affect the mass transport rates through the polymer as well as the polymer processing characteristics and the stability of the dosage form. Below the glass transition temperature, the polymer will exist in an amorphous, glassy state. When exposed to temperatures above T_g, the polymer will experience an increase in free volume that permits greater local segmental chain mobility along the polymer backbone. Consequently, mass transport through the polymer is faster at temperatures above T_g. Often, polymer processing, such as extrusion or high-shear mixing, is performed above T_g. On the other hand, the greatest stability during storage of a polymer device may be obtained at temperatures below T_g, where solute diffusion is much slower and more subtle changes in polymer properties (e.g., tackiness) are reduced.

The presence of plasticizers, such as residual solvent or dissolved solutes including the drug or other additives, will tend to lower polymer T_g. Conversely, features that hinder segmental motion along the polymer, such as greater chain rigidity, bulky side groups, and ring structures, would tend to increase T_g. Finally, the presence of charged groups on a polymer can also influence drug release from the device. The number and density of ionized groups along the polymer backbone, on the side-chain groups, or at the terminal end-groups of the polymer chains can all vary the extent of polymer–polymer and polymer–drug interactions. In this manner, ionizable groups can affect drug solubility in the polymer and, correspondingly, the release rate from the polymer. A number of reviews which describe in detail of the relationship between polymer properties and performance in drug delivery applications have been published (33, 34).

FACTORS AFFECTING DRUG RELEASE

Aside from the physicochemical properties of the polymer itself, there are additional factors that can influence drug

Table 2 Properties affecting polymer selection, manufacture, and performance

Property	Examples
Regulatory and toxicology status	
Monomer or copolymer composition	
Molecular weight	M_w, M_n
Molecular weight distribution	Polydispersity ratio (M_w/M_m)
Molecular architecture	Linear polymers Branched polymers Crosslinked network
Tacticity	Isotactic Syndiotactic Atactic
Secondary structural attributes	Helicity beta-structure
Morphology	Amorphous Semicrystalline Crystalline
Thermal transition temperatures	Melting temperature, T_m Glass transition temperature, T_g
Ionization	Side-chains Main-chain end groups

release and the performance characteristics of the dosage form. Examples of these factors are highlighted in Table 3. Dosage forms can be formulated into a wide range of geometries and physical forms and sizes. The appropriate selection would depend on the flexibility with which a polymer can be processed, the desired route of administration, the duration of action, and the stability of the drug under processing conditions. Additionally, the drug distribution in the dosage form can be either homogeneous (a monolithic or matrix system) or heterogeneous (reservoir system). Finally, the rate and mechanism by which the polymer degrades can also influence drug release and, potentially, drug stability following administration. If necessary, systems can be designed so that release of the drug load is completed before polymer degradation begins to affect the integrity of the dosage form. Conversely, a dosage form can also be designed in a way that polymer degradation and device erosion can both contribute to drug release.

Based on the above reasons, polymers possessing a variety of degradation rates and mechanisms have been developed; however, hydrolysis still remains the predominant degradation mechanism for polymers that are most commonly used in drug delivery applications. Many polymers that are susceptible to hydrolysis, for example, the polyesters PLA and PLG, degrade by random hydrolysis that takes place homogeneously throughout the bulk of the polymer device. In contrast, other classes of polymers, such as the polyanhydrides and polyorthoesters, have been developed in an attempt to yield hydrolysis only at the outer surface of the device that is exposed directly to the aqueous environment. When this so-called surface-erosion process is achieved, hydrolysis is believed to take place in a heterogeneous manner, and the polymer device degrades from the outside toward the center.

Reservoir systems are designed to have the drug deposited inside of a polymer membrane. In such systems where the polymer membrane serves as the barrier, drug release is controlled by Fickian diffusion of the drug

Table 3 Device attributes affecting performance

Property	Attribute	Examples
Design of delivery device	Shape/geometry	Cylinder or rod Microparticles (microsphere, microcapsule, nanoparticle) Film or sheet Viscous gel or liquid
	Drug distribution	Homogeneous (matrix or monolithic system) Heterogeneous (reservoir system)
	Formulation	Drug loading Excipients Porosity
Degradation	Rate	
	Mechanism	Homogeneous degradation (bulk) Heterogeneous degradation (surface-erosion)

through the membrane, and the release rate can be described by the following relationship:

$$\frac{dM_t}{dt} = \frac{ADC_s}{t_m} \quad (1)$$

where M_t is the mass of drug released at time t, A is the surface area of the barrier membrane, D is the diffusion coefficient of the drug in the membrane, C_s is the solubility of the solute in the polymer, and t_m is the membrane thickness (35). As long as the drug concentration in the reservoir remains well above saturation and the membrane thickness is small relative to the other dimensions of the device, this relationship indicates that the drug release rate should be constant over time (zero-order) so long as release was diffusion controlled. Because biodegradable polymers are chemically unstable, they are generally not used to prepare reservoir delivery systems. The potential for these polymers to degrade prematurely thereby releasing the remaining contents of the drug reservoir presents a safety concern.

More typically, therefore, biodegradable polymers are used to prepare matrix (monolithic) systems in which the drug is dispersed or dissolved homogeneously throughout the polymer. Matrix systems can be prepared in a multitude of forms including films, sheets, cylinders, rods, and microparticles (e.g., microspheres and nanospheres). Drug is initially released from the exposed, outer surfaces of this type of dosage form. As these regions become depleted of drug, release continues as drug is transported from increasingly deeper regions of the dosage form. Because the diffusional path length gets continuously longer during the release process, diffusion-controlled release from matrix systems is not zero-order. Based on a thin-slab geometry, Higuchi derived a relationship which, when differentiated, yields the following prediction for the diffusion-controlled release rate from a matrix system (35):

$$\frac{dM_t}{dt} = \frac{A}{2}\left(\frac{DS_s(2C_L - C_s)}{t}\right)^{\frac{1}{2}} \quad (2)$$

where A is the area of the polymer slab, C_L is the drug loading in the device and the remaining variables are the same as defined in Eq. (1). This relationship suggests that when diffusion-controlled release is achieved, the drug release rate will decrease proportionately with $t^{-1/2}$, assuming that polymer degradation does not contribute to drug release.

Results obtained by quantitatively monitoring drug release from monolithic matrix systems indicate that low-molecular-weight drugs can be released at rates that are consistent with a diffusion-controlled mechanism. High-molecular-weight drugs such as peptides and proteins, however, generally have little permeability through the polymer phase due to their low polymer solubility and diffusion rates. Consequently, these molecules are unlikely to be released from monolithic systems by purely diffusion-controlled mechanisms. Instead, release of peptides and proteins from polymer matrices needs to be aided by additional mechanisms that can facilitate mass transport out of the device (36). For example, release can be enhanced by the formation of pores or channels that are created by the continuous dissolution and removal of soluble components, such as the drug or other formulation excipients, from the polymer matrix. Alternatively, drug release can also be enhanced by polymer degradation and the subsequent erosion of the device itself. A variety of mathematical models have been proposed to correlate the effects of both polymer degradation and drug diffusion on the overall release rate (20, 37, 38).

In a special case, novel systems have been developed that are capable of providing zero-order drug release profiles. Surface-eroding polymers in which polymer degradation takes place only at the outer surfaces of the device have been prepared. When drug release can be limited to regions undergoing degradation, a constant drug release profile is possible. In this case, the polymer degradation rate can be used to control the release rate of the drug. Hopfenberg developed a mathematical model to correlate this type of drug release system so long as the surface area remains constant during the degradation process (39). The cumulative fraction of drug released at time t was described by:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_0 t}{C_L a}\right)^n \quad (3)$$

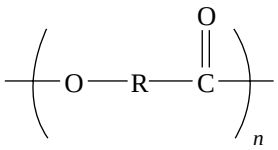
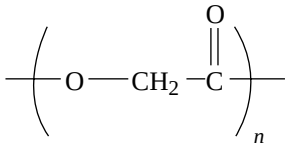
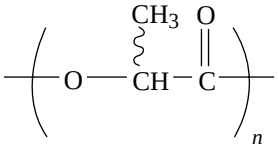
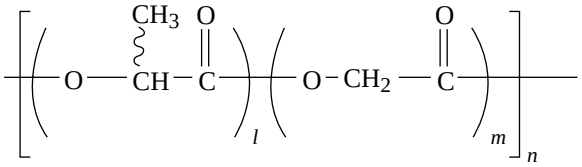
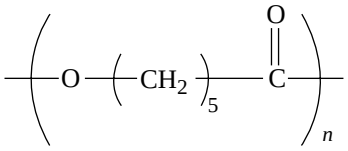
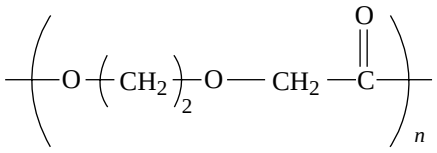
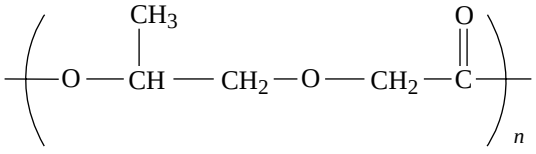
where k_0 is the zero-order rate constant describing the polymer degradation (surface-erosion) process, C_L is the initial drug loading throughout the system, a is the system half-thickness(i.e., the radius for a sphere or cylinder), and n is an exponent that varies with geometry [$n = 1$, 2, and 3 for slab (flat), cylindrical, and spherical geometry, respectively] (39).

COMMON CLASSES OF BIODEGRADABLE POLYMERS

Polyesters

A variety of hydrolytically labile polyesters have been evaluated in drug delivery applications. Several

Table 4 Common polyester structures

Polyester linkage	
poly(glycolide), PGA	
poly(D,L-lactide), PLA	
poly(D,L-lactide-co-glycolide), PLG	
poly(ε-caprolactone)	
poly(dioxanone)	
poly(hydroxybutyrate)	

examples are listed in Table 4. Among these, however, poly (glycolide), poly(lactide), and various copolymers of poly(lactide-co-glycolide) are the ubiquitous choice because of their proven safety and lack of toxicity, their wide range of physicochemical properties, and their flexibility to be processed into a variety of physical dosage forms. These polymers and copolymers are prepared by anionic ring-opening reaction of highly purified glycolide and lactide monomers, the cyclic dimers of glycolic acid and lactic acid, respectively. Stannous octoate (tin(II) 2-ethyl hexanoate) is the chain initiator most commonly used in the synthesis of polymers for pharmaceutical applications. Because the lactide monomer possesses two chiral carbons, polymerization may be performed using D-lactide (the D-,D-cyclic dimer), L-lactide (the L-,L- cyclic dimer), or the meso-lactide (the D-,L- cyclic dimer). Synthesis of poly(D,L-lactide) (PLA), though, is most commonly performed by copolymerization of a racemic mixture of the D- and L-lactide monomers. In a similar manner, the copolymer poly(D,L-lactide-co-glycolide) (PLG) is generally prepared using varying ratios of the glycolide to a racemic blend of D-/L-lactides. Because PLA and PLG are prepared from distinct monomer species, there exists the possibility that polymerization may result in a nonrandom sequence of monomer species (21). Compositional heterogeneity can lead to variability in properties between polymer lots. Historically, this has been problematic for PLG polymers containing 50% glycolide (50:50 PLG).

Homopolymers of poly(D-lactide) and poly(L-lactide) tend to be semi-crystalline. As a result, water transport into these polymers is slow. Because of the slow uptake of water and the structural integrity introduced by crystallites, degradation rates of these polymers tend to be relatively slow (i.e., 18–24 months) (21). In contrast, poly(D,L-lactide) (PLA) is amorphous and is observed to degrade somewhat faster (i.e., 12–16 months). Adding increasing proportions of glycolide into PLA lowers T_g and generally increases polymer hydrophilicity. These PLG copolymers generally remain amorphous as long as the glycolide content remains within the range of about 0–70 mole%. In contrast, poly(L-lactide-co-glycolide) is amorphous when the glycolide content is 25–70 mole%. The most rapid degradation rate (i.e., 2 months) is observed in PLG copolymers containing 50% glycolide. Poly(glycolide), despite being semi-crystalline, is found to degrade relatively fast (i.e., 2–4 months) even compared to the amorphous PLA. This is attributed to the much greater hydrophilicity of the glycolide over the lactide. Actual degradation times, though, will depend on environmental conditions, polymer molecular weight, system geometry and morphology, and processing conditions (21, 40, 41).

After exposure to and equilibration in an aqueous environment, polyesters degrade by hydrolysis that occurs homogeneously throughout the bulk of the polymer device. Evidence commonly used to support such a conclusion is that the bulk degradation of the polymer device (as indicated by weight loss) lags behind the decrease in polymer molecular weight over time (Fig. 4). However, other studies have provided evidence of nonhomogeneous hydrolytic degradation under certain circumstances. Devices prepared from amorphous polyesters including PLA and 75:25 PLG have been reported to exhibit accelerated degradation within the interior of the device (42). This phenomenon has been attributed to acid-catalyzed polymer hydrolysis resulting from the build-up in these regions of acidic oligomers and monomers during the degradation process. In these instances, the devices are either large in physical dimensions or they are nonporous, meaning that the acidic by-products cannot be readily washed away from the interior of the device. Alternatively, heterogeneous degradation in semi-crystalline polymers such as poly(glycolide) results from the preferential diffusion of water into the amorphous regions. As a result, degradation occurs in the amorphous regions leaving behind crystalline-rich portions that hydrolyze more slowly (43, 44). Initially amorphous polymers such as PLA and 75:25 PLG have also been found to exhibit heterogeneous degradation, reportedly through the crystallization of polymer fragments rich in L-lactide during the course of hydrolysis (43).

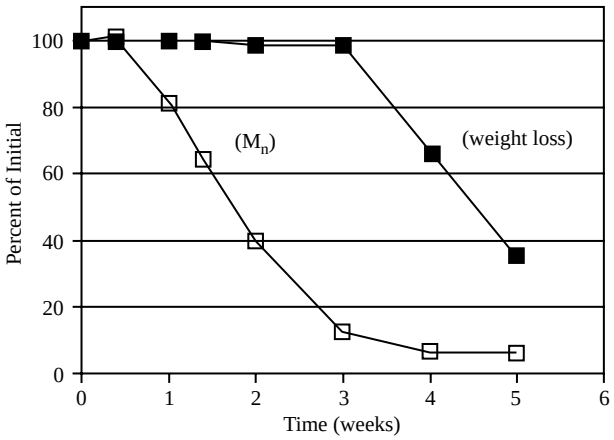


Fig. 4 Degradation profiles of cylindrical PLG rods incubated at 37°C in vitro. Degradation is exhibited by the percent change over time of the sample weight, ■, and number-average molecular weight (M_n), □. (Adapted from Ref. 25.)

Many reviews describing the development of polyester-based biodegradable drug delivery systems have been published (21, 22, 40, 22, 45). Much work has been performed in evaluating these materials for delivery of proteins (36) and vaccines (46). More recently, novel chemical and engineering approaches have been discovered to make crosslinked hydrogels and three-dimensional porous matrices for a wide range of biomedical applications including, protein and gene delivery as well as cell therapy.

Polyanhydrides

Historically, polyanhydrides were developed in the textile industry during the first half of the 20th century as alternate fiber materials (47, 48). However, the modern polyanhydrides that are currently under investigation as drug delivery platforms represent a novel class of polymer that, unlike the polyesters, has been specifically developed for biodegradable applications. In particular, these polyanhydrides were specifically prepared in attempts to produce surface-eroding dosage forms.

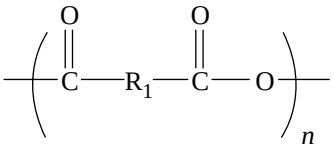
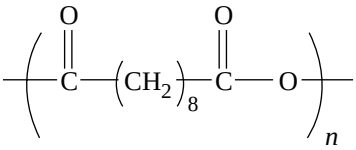
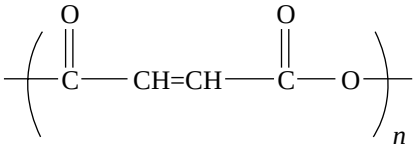
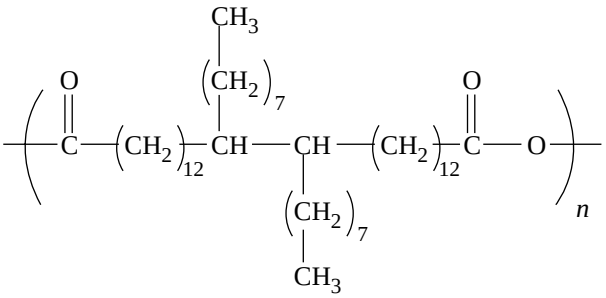
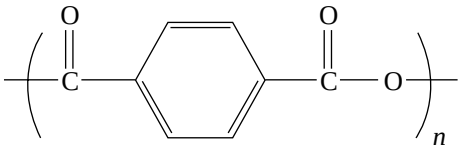
The anhydride linkages of these polymers are, in general, more hydrolytically labile than the polyester bond. In order to achieve a surface-eroding mechanism, polymers are generally prepared from very hydrophobic monomers in order to minimize water penetration into the bulk of the device. By doing this, hydrolysis of the labile anhydride linkages would be restricted to the outer exposed surfaces of the polymer device. A wide variety of aliphatic and aromatic monomers have been used to prepare surface-eroding polyanhydride polymers (Table 5). Aliphatic polyanhydrides are normally prepared from dicarboxylic acids such as adipic acid, sebacic acid (SA), dodecanoic acid, and fumaric acid (FA). Additionally, diacidic fatty acid monomers (fatty acid dimers, or FAD) have also been used. Polymers with increasing hydrophobicity can be made from aromatic monomers including phthalic acid and various carboxyphenoxy-alkanes such as CPM, CPP, and CPH (Table 5). High-molecular-weight polyanhydrides are usually synthesized by first converting the dicarboxylic acid monomer to mixed anhydride prepolymers using acetic anhydride followed by polymerization of prepolymers using polycondensation reaction in the melt.

Typically, homopolymers are not studied because they possess unfavorable characteristics rendering their handling and manufacture difficult. Poly(SA), poly(CPP), and poly(FA) are semicrystalline and thus suffer from either being brittle or having high T_m. Conversely, poly(FAD) is a liquid. Therefore, polyanhydrides are often prepared as copolymers of aliphatic and/or aromatic monomers. The most common copolymers under investigation in drug delivery applications include poly(FAD-SA) and poly(CPP-SA).

Studies on aliphatic polyanhydrides have shown that increasing the alkyl chain length (e.g., from $n = 4$ to 12) of the dicarboxylic acid monomers increases polymer hydrophobicity resulting in a decrease in both polymer degradation and drug release rates (49). These trends in degradation were observed both in vitro and in vivo. While poly(FAD) is amorphous, the degree of crystallinity observed in poly(FAD-SA) copolymers increased directly once the SA content was raised above 30 mole%. In spite of this, raising the SA content has been shown to increase the degradation rate. This can be attributed to the greater hydrophilicity of SA relative to FAD (50). In contrast, poly(CPP-SA) copolymers are semicrystalline across the entire range of composition, yielding the lowest degree of crystallinity when the SA content is between 15 and 70 mole%. While having little influence on polymer crystallinity, changes in copolymer composition can affect polymer degradation rates. Figure 5 shows the relative in vitro degradation rates of poly(CPP-SA) copolymers containing 0–79 mole% SA. In these samples, degradation of 100% poly(CPP) was estimated (by extrapolation) to require over 3 years, whereas copolymers containing the highest amounts of SA degraded as quickly as 1–2 weeks. The initial motivation for synthesizing polyanhydrides was to prepare devices that degrade at a constant rate by a surface-erosion process. To this end, nearly zero-order degradation profiles were achieved for over a 6-day period for discs prepared from poly(SA) and also from poly(CPP-SA) containing 80 and 20% SA. Similarly, poly(CPP) and 85:15 poly(CPP-SA) also showed constant degradation profiles that lasted for a period of several months.

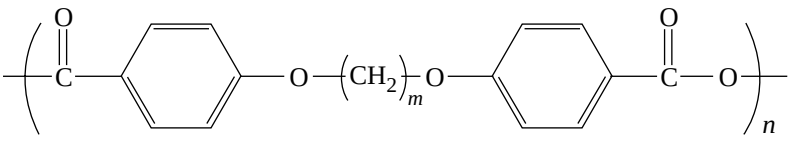
Degradation of poly(FAD-SA) has also been reported to be nearly zero-order based on the rate of SA release from the polymer (50). However, evidence suggests that devices prepared from these polymers do not necessarily degrade by a purely surface-erosion mechanism. Cumulative release profiles of individual monomers released from a degrading poly(CPP-SA) matrix indicated that SA was released at a much faster rate than was CPP. Other studies have shown that, similar to certain polyesters, amorphous regions in poly(CPP-SA) will preferentially hydrolyze first, leaving behind a network of pores surrounding the remaining crystalline-rich structures (48). These findings suggest that while polyanhydrides are able to provide degradation behavior that is consistent with a surface-erosion mechanism, the actual processes involved in polymer degradation and erosion of the device can be more complicated.

Table 5 Common polyanhydride structures

Polyanhydride linkage	
poly(sebacic acid), SA	
poly(fumaric acid), FA	
poly(erucic acid dimer) or poly(FAD), (FAD, fatty acid dimer)	
poly(terephthalic acid), TA (para-) poly(isophthalic acid), IPA (meta-)	

poly[bis(*p*-carboxyphenoxy) alkanes]

m = 1	poly[1-bis(*p*-carboxyphenoxy)methane],	CPM
m = 3	poly[1,3-bis(*p*-carboxyphenoxy)propane],	CPP
m = 6	poly[1,6-bis(*p*-carboxyphenoxy)hexane],	CPH



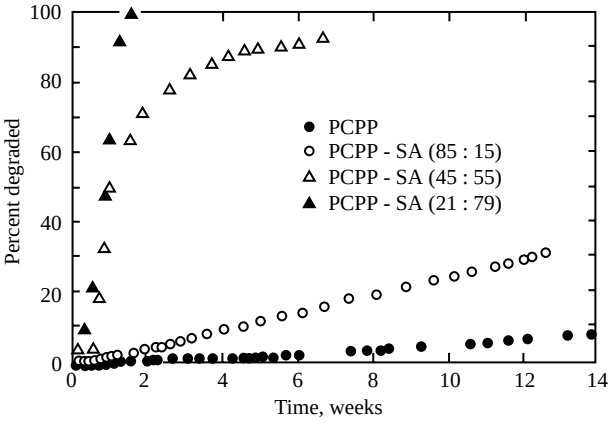


Fig. 5 Degradation profiles (percent weight loss) of compression-molded poly[bis(*p*-carboxyphenoxy) propane anhydride] (PCPP) containing varying ratios of sebacic acid (SA). The copolymers were incubated in 0.1M pH 7.4 phosphate buffer at 37°C. (From Ref. 47.)

The release of a number of drugs from polyanhydride matrices has been studied including ciprofloxacin (49), *p*-nitroaniline (47, 51), cortisone acetate (51), insulin (51), and a variety of proteins (50). In many instances, drug release was reported to coincide with polymer degradation. The biocompatibility of polyanhydrides has also been assessed in a number of studies (51–54). The only commercial product that has received regulatory approval is Gliadel®. This product is a thin wafer (1.45 cm in diameter, 1 mm in thickness) containing 7.7 mg carmustine(BCNU), and is prepared from 20:80 poly(CPP-SA). As many as 8 wafers are implanted in the cavity created after surgical removal of recurrent glioblastoma multiforme, an aggressive form of brain cancer. Studies show that BCNU release from Gliadel® wafers is controlled by both drug diffusion and erosion of the polyanhydride matrix (55).

Polyorthoesters

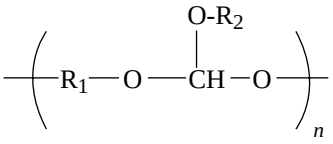
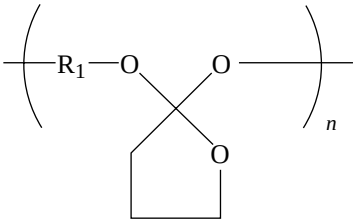
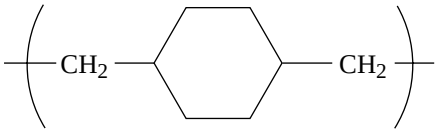
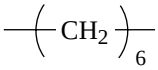
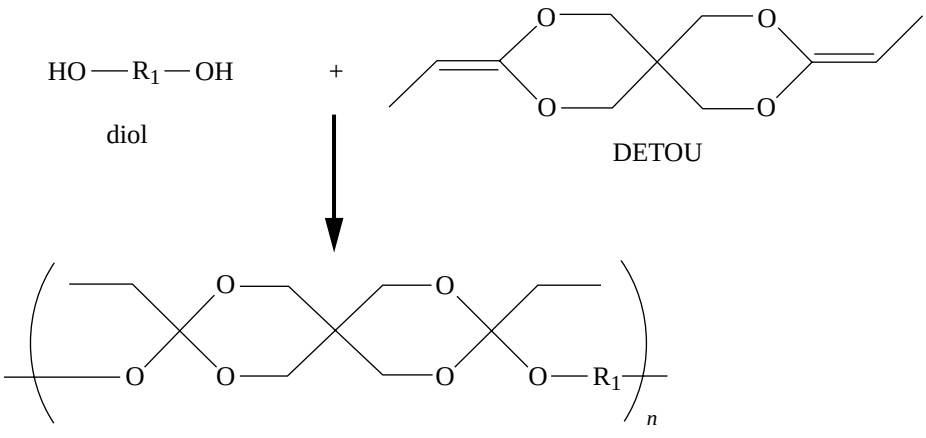
A series of polyorthoesters has been under development since 1970 in efforts to prepare surface-eroding biodegradable polymers specifically for drug delivery applications (56–61). The first hydrolytically labile polyorthoesters were synthesized by polycondensation of a diol (either 1,6-hexanediol, HD, or *cis/trans*-1,4-cyclohexane dimethanol, CHDM) with an orthoester (diethoxy tetrahydrofuran, DETHF). This polymer was initially called Chronomer™ and was developed at the Alza Corporation (Palo Alto, CA) by Choi and Heller (Table 6). Later the name was changed to Alzamer®; development of these polymers has since been discontinued. Hydrolysis of Alzamer® produces the corresponding diol along with γ-hydroxybutyrolactone which rapidly opens its ring structure to form γ-hydroxybutyric acid. Because polymer hydrolysis was acid catalyzed, production of this by-product accelerated the rate of degradation of the remaining polymer. In order to avoid catastrophic self-accelerated hydrolysis, the polymer was usually stabilized by the addition of an inorganic base such as sodium carbonate.

In attempts to overcome the limitations of these polymers, Heller developed alternate polyorthoesters at SRI International (Palo Alto, CA). The second generation polyorthoesters were prepared by the addition of a diol with the cyclic diketene acetal, 3,9-diethylidene-2,4,8, 10-tetraoxaspiro [5.5] undecane (DETOU) (Table 5). When prepared with varying ratios of these two diols (i.e., HD and CHDM), polyorthoesters possessing a wide range of mechanical properties could be obtained. Increasing the HD composition from 0 to 100% lowered the polymer T_g from over 100°C to about 20°C accordingly (57). In addition, the T_g of DETOU polyorthoesters can be further reduced by synthesis using linear diols of successively longer alkyl chain length. Increasing the alkyl length from $n = 6$ to $n = 12$ lowers T_g from 20 to 0°C (59). The reduction in glass transition temperatures of these polymers reflects the increased chain flexibility of the diol component.

DETOU polyorthoesters, because of the hydrophobic nature of the monomers are found to degrade relatively slowly in vitro with only 15% weight loss after about 150 days and 60% weight loss after 325 days. These polymers are also shown to hydrate slowly (i.e., adsorbing about 0.3–0.75 wt% of water). While degradation of the DETOU polyorthoester is also acid-catalyzed, the degradation products do not generate any acidic species. Heller suggested that a faster polymer degradation could be achieved by the addition of acidic excipients into the polymer matrix. When 1 wt% suberic acid was added to a DETOU polyorthoester polymer prepared with 1,6-hexanediol, a complete release of naltrexone pamoate was achieved in vitro in 30 days (57). Conversely, the polymer can be stabilized against hydrolysis by the addition of a base such as magnesium hydroxide.

One potential limitation to the use of blended excipients to regulate polymer degradation rates is the likelihood that the excipient could diffuse out of the device before polymer degradation has terminated. For acidic additives, this would cause polymer erosion to slow down significantly, meaning that polymer residues would remain in the implanted tissue site for a long time. To avoid this possibility, novel approaches have been developed to

Table 6 Common polyorthoester structures

Polyorthoester linkage	
Polyorthoester I, with:	
R_1 = *cis/trans*-cyclohexyl dimethanol, CHDM:	
R_1 = 1,6-hexanediol, HD:	
Polyorthoester II (synthetic scheme)	

retain acidic species within the polymer. For example, hydrolytically labile ester bonds have been incorporated into the polymer network. Degradation of these groups produced acidic species that remained covalently attached to that polymer system over time.

Reaction of a triol such as 1,2,6-hexanetriol with a DETOU prepolymer permits the formation of a crosslinked network. Rod-shape polymer systems (2.4 mm in diameter) were fabricated containing 30 wt% levonorgestrel and 7 wt% micronized $Mg(OH)_2$ as a stabilizer. These devices contained 1 wt% 9,10-dihydroxystearic acid to modify polymer erosion rate. SEM photomicrographs of the rods show evidence of surface erosion following implantation for up to 16 weeks. A degradation zone is observed to move progressively toward the center of the rod while, at the same time, erosion causes this region to become increasingly more porous as the polymer continues to degrade (56).

Heller and colleagues at Advanced Polymer Systems (Redwood City, CA) continue to develop additional polyorthoesters with a variety of physical properties and potential applications (60, 61). Generally speaking, polyorthoesters do possess the potential to exhibit surface-eroding behavior. However, several issues that may limit the commercial application of this class of polymers are still present. One issue is that synthesis of these polymers involves complicated monomers and polymerization chemistry. The second issue is, to date, the toxicology and biocompatibility of these polymers and their degradation products have not yet been fully characterized. Finally, the requirement for pH-regulating additives such as acids and bases can be undesirable in applications where the drug stability is affected.

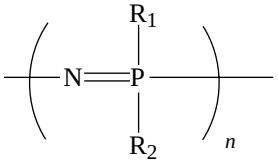
Phosphorus-Containing Polymers

There are two common classes of phosphorus-containing polymers, the phosphazenes (Table 7) and phosphoesters (Table 8). In both cases, polymers possessing a range of chemical, physical, and mechanical properties can be synthesized through simple changes in monomer side-chain substitution. Polyphosphazenes contain alternating phosphorus-nitrogen double and single bonds and are synthesized by reaction of poly(dichlorophosphazene) with organic nucleophiles such as alkoxides, aryloxides, or amines (62, 63). Polymer prodrugs have been prepared in which the drug entity is covalently attached to the polyphosphazene. Examples of these systems include the drugs procaine, benzocaine, and heparin. More typically, however, side-chain substituents are selected in order to vary polymer hydrophobicity as well as the hydrolytic stability of the phosphazene bond. Copolymers containing varying ratios of imidazole and methylphenoxy side-chains have been prepared (Table 7) (62). Increasing the imidazole content of these polymers increases the reactivity toward hydrolysis of the phosphazene linkages. After 600 hours in phosphate buffer, a polyphosphazene containing 20% imidazole lost only 4% weight due to degradation, whereas another polymer containing 45% imidazole lost over 30% weight. The suitability of these polymers as drug delivery platforms was evaluated using *p*-nitroaniline, progesterone, and bovine serum albumin as model drugs (62).

Polyphosphazenes have also been prepared using modified amino acid ester side-chain substituents (63) (Table 7). Studies show that the polymer containing the smallest hydrophobic side-chain constituent, glycine ethyl ester, exhibited the most rapid degradation. This was attributed to the lower steric hindrance that the small side-chain group could provide in protecting the phosphazene bond from hydrolytic attack. Cast films of this polymer were degraded in vitro by 40% (as determined by percent mass loss) after 1200 hours (50 days), whereas polymers containing longer amino acid side-chain constituents such as alanine ethyl and benzylalanine ethyl esters lost only 10–15% weight during the same time interval. Substitution at the α-carbon of the amino acid side-chain, therefore, seemed to provide a greater influence on the rate of polymer hydrolysis than the overall hydrophobicity of the ester substituent. Characterization of polymer degradation products indicated that these polymers degraded to phosphates, glycine or alanine, ethanol or benzyl alcohol, and ammonia. Drug release, as was demonstrated using ethacrynic acid and the azo dye Biebrich Scarlet, followed the same trends as did polymer degradation whereby the fastest release rates were exhibited by the glycine ethyl ester polymer. Polyphosphazenes have been studied for the delivery of proteins (64), naproxen (65, 66) and colchicine (67), as well as in periodontal treatments (68).

The class of phosphoester-based polymers includes polyphosphates, polyphosphonates, and polyphosphites (Table 8). A series of phosphoesters based on bisphenol A (BPA) have been prepared and evaluated in drug delivery applications (69, 70). Polymerization was carried out by interfacial polycondensation reaction of the diol (BPA) with a phosphodichloridate. Selection of either an alkyl- or alkoxide-substituted dichloridate resulted in the synthesis of either the phosphonate or phosphate polymer, respectively. High-molecular-weight polymers (M_w between 20–40 kDa) with T_g of 103–115°C were synthesized. The uptake of water and swelling of these polymers, both in vitro and in vivo, increased with the increasing relative

Table 7 Common phosphorus-containing polymers — polyphosphazenes

Polyphosphazene linkage	

R_1 and R_2 side-chain substituents:

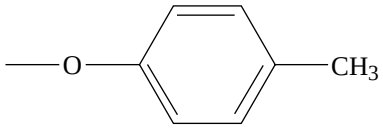
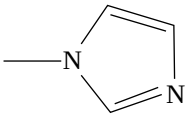
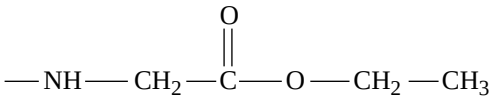
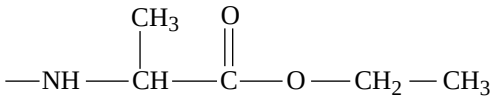
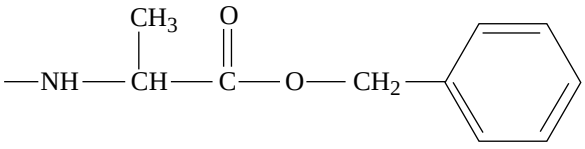
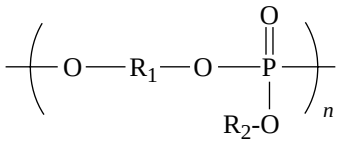
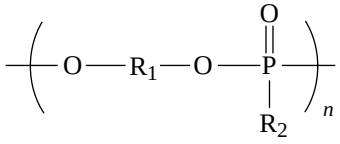
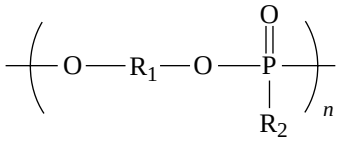
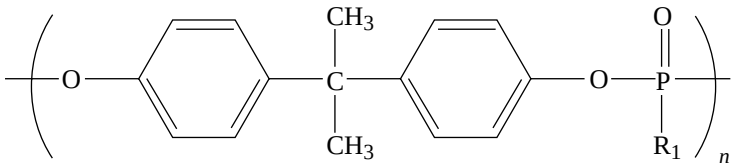
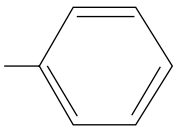
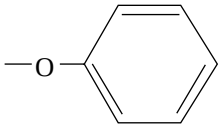
methoxyphenoxy	
imidazole	
ethyl glycine	
ethyl alanine	
ethyl benzylalanine	

Table 8 Common phosphorus-containing polymers — polyphosphoesters

Polyphosphate linkage	
Polyphosphonate linkage	
Polyphosphite linkage	

bisphenol A (BPA) polyphosphoesters



BPA-EP, poly(ethyl phosphonic acid-BPA)	R_1 =	$-CH_2-CH_3$
BPA-EOP, poly(ethyl phosphate acid-BPA)	R_1 =	$-O-CH_2-CH_3$
BPA-PP, poly(phenyl phosphonic acid-BPA)	R_1 =	
BPA-POP, poly(phenyl phosphate acid-BPA)	R_1 =	

hydrophilicity of the phosphate substituent. The aliphatic polyphosphate BPA-EOP exhibited the greatest water uptake and swelling during degradation, whereas the aromatic polyphosphonate BPA-PP exhibited the least. Degradation rates increased with polymer hydrophilicity. For example, the percentage weight loss in BPA-EOP and BPA-PP samples was 35 and 10%, respectively, following implantation in rabbits for 30 weeks.

Other diols have been used to prepare polyphosphoesters including1,4-bis(hydroxyethyl)-terephthalate (BHET) and *trans*-cyclohexane dimethanol (T-CHDM). The synthesis and characterization of various polyphosphoesters have recently been reviewed (71). Of particular interest is a polyphosphoester prepared by polycondensation of an oligomeric polyester diol with ethylphosphodichloridate (EOP). In this case, the diol pre-polymer was synthesized using ethylene glycol or 1,2-propylene glycol to initiate the ring-opening condensation reaction of a cyclic lactide. This polymerization was carried out in order to prepare a low-molecular-weight oligomeric polyester diol that was then polymerized with EOP. The product, actually a poly(lactide-co-phosphate), exhibited faster degradation as the phosphate content increased. This polymer is currently being investigated by Guilford Pharmaceuticals (Baltimore, MD) for delivery of the chemotherapeutic agent paclitaxel (72).

NEW DIRECTIONS

A wide variety of approaches are continuously being pursued in the quest for improved biodegradable drug delivery systems. New and modified polymer chemistries that offer distinctive degradation and drug delivery attributes are being identified and evaluated. At the same time, innovative engineering and manufacturing methods are under development to fabricate devices and physical platforms having novel three-dimensional structural attributes. In certain instances, these products make it possible to treat entirely new therapeutic applications using biodegradable devices. One approach is through the preparation of biodegradable crosslinked polymer networks. When crosslinking is carried out using hydrophilic polymers, hydrogels that absorb a significant amount of water (for example, greater than 10 wt%) can be produced. Crosslinking can generally be achieved via three different means: by formation of covalent bonds, by ionic interactions, and by formation of highly entangled chain networks. Degradation of crosslinked polymer networks can take place by either breaking the crosslinks or the polymer backbone bonds, or by slow disentanglement and dissolution of the polymer network. The highly swollen, three-dimensional structure of hydrogels has been an attractive feature to researchers in developing delivery systems for macromolecular drugs. A number of polymers derived from naturally-occurring constituents including alginate (73), dextran (74), collagen (75), gelatin (76), and albumin (77) have been employed to prepare hydrogels. Alternatively, proven biocompatible polymers such as PLA and PLG (78) and poly(γ-benzyl-L-glutamic acid) (79) have also been used to prepare crosslinked, synthetic hydrogels. In addition, a variety of biodegradable hydrogels based on other types of constituents have also been synthesized (80).

New approaches have been taken to design and engineer novel biodegradable drug delivery platforms. Highly porous polymer platforms with controlled pore density and size have recently been synthesized by the formation of either sponge-like or entangled fibrous matrices (81, 82). These systems are currently being investigated as extracellular matrices for cell therapy. Matrices loaded with viable cells capable of releasing bioactive agents are being investigated as implantable artificial organs. In certain studies, hepatocytes incorporated into PLA matrices were shown to remain viable for 14 days. In other studies, transplanted hepatocytes were shown to be capable of forming new liver-like tissue (83). Another example is the artificial pancreas in which the islet cells were incorporated into fibrous PGA matrices for the glucose-responsive release of insulin (84). Other polymers, such as polyphosphazene, have also been investigated for cell therapy (85), while alginate hydrogels have been explored for islet transplantation (86). The implantation of biodegradable polymer platforms seeded with osteoblast cells (87) or incorporated with bone-derived growth factors(88) have been studied for induction of skeletal tissue growth. The growing applications of biodegradable polymer scaffolds in cell therapy and tissue engineering have been recently reviewed in several articles (81, 83, 89, 90).

SUMMARY

This is an exciting time for the development of biodegradable drug delivery platforms. The sustained delivery of drugs to the body has, practically speaking, become a reality as numerous products have passed regulatory review and proven to be commercially successful. New polymers continue to be developed while, at the same time, new therapeutic applications are being increasingly recognized.

REFERENCES

1. Robinson, J.R.; Lee, V.H.L. *Controlled Drug Delivery*; From Series: Drugs and the Pharmaceutical Sciences Marcel Dekker, Inc.: New York, 1987; 29.
2. Banker, G.S. Pharmaceutical Applications of Controlled Release – An Overview of the Past, Present, and Future. *Medical Applications of Controlled Release*; Langer, R.S., Wise, D.L., Eds.; CRC Press: Boca Raton, Florida, 1984; II.
3. *Physicians Desk Reference*, 53rd Ed.; Medical Economics Company, Inc.: Montvale, New Jersey, 1999.
4. Fraser, I.S.; Tiitinen, A.; Affandi, B.; Brache, V.; Croxatto, H.B.; Diaz, S.; Ginsburg, J.; Gu, S.; Holma, P.; Johansson, E.; Meirik, O.; Mishell, D.R.; Nash, H.A.; von Schoultz, I.; Sivin, I. Norplant® Consensus Statement and Background Review. Contraception **1998**, *57*, 1–9.
5. Harrison, P.F.; Rosenfield, A. Research, Introduction, and Use: Advancing from Norplant. Contraception **1998**, *58*, 323–334.
6. Heller, J. Biodegradable Polymers in Controlled Drug Delivery. Critical Reviews in Therapeutic Drug Carrier Systems **1984**, *1* (1), 39–90.
7. Pitt, C.G.; Schindler, A. Biodegradation of Polymers. *Controlled Drug Delivery*; Bruck, S.D., Ed.; CRC Press: Boca Raton, Florida, 1983; 1.
8. Sidman, K.R.; Schwope, A.D.; Steber, W.D.; Rudolph, S.E. Use of Synthetic Polypeptides in the Preparation of Biodegradable Delivery Systems for Narcotic Antagonists. NIDA Research Monograph **1981**, *28*, 214–231.
9. Charles, E.L.; Buffalo, N.Y. U.S. Patent 2,668,162, 1954(to E.I. DuPont de Nemours).
10. Schmitt, E.E.; Polistina, R.A. U.S. Patent 3,297,033, 1967(to American Cyanamid).
11. Kulkarni, R.K.; Pani, K.C.; Neuman, C.; Leonard, F.; Polylactic Acid for Surgical Implants, Technical Report 6608, Walter Reed Army Medical Center (Project 3A013001A9-1C), 1966.
12. Wasserman, D. U.S. Patent, 3,375,008,1971.
13. Yolles, S.; Eldridge, J.E.; Woodland, J.H.R. Sustained Delivery of Drugs from Polymer/Drug Mixtures. Polym. News **1970**, *1*, 9–15.
14. Yolles, S.; Leafe, T.D.; Meyer, F.J. Timed-release Depot for Anticancer Agents. J. Pharm. Sci. **1975**, *64* (1), 115–116.
15. Yolles, S.; Leafe, T.; Ward, L.; Boettner, F. Controlled Release of Biologically Active Drugs. Bull. Parent. Drug Assoc. **1976**, *30* (6), 306–312.
16. Yolles, S.; Woodland, J.H.R. Long-acting Delivery Systems for Narcotic Antagonists.1. **1973**, *16* (8), 897–901.
17. Wise, D.L. Controlled Release for Use in Treatment of Narcotic Addiction. *Medical Applications of Controlled Release*; Langer, R., Wise, D.L., Eds.; CRC Press: Boca Raton, Florida, 1984; II.
18. Schwope, A.D.; Wise, D.L.; Howes, J.F. Development of Polylactic/glycolic Acid Delivery Systems for Use in Treatment of Narcotic Addiction. NIDA Research Monograph **1976**, *4*, 13–18.
19. Kronenthal, R.L. Biodegradable Polymers in Medicine and Surgery. *Polymers in Medicine and Surgery*; From series, Kronenthal, R.L., Oser, Z., Martin, E., Eds.; Polymer Science and Technology; Plenum Press: New York, 1975; 8.
20. Heller, J.; Baker, R.W. Theory and Practice of Controlled Drug Delivery from Bioerodible Polymers. *Controlled Release of Bioactive Materials*; Baker, R., Ed.; Academic Press: New York, 1980; 1–17.
21. Lewis, D.H. Controlled Release of Bioactive Agents from Lactide/Glycolide Polymers. Drugs Pharm. Sci. **1990**, *45*, 1–41.
22. Holland, S.J.; Tighe, B.J.; Gould, P.L. Polymers for Biodegradable Medical Devices. 1. The Potential of Polyesters As Controlled Macromolecular Release Systems. J. Control. Rel. **1986**, *4*, 155–180.
23. Crotts, G.; Park, T.G. Protein Delivery from Poly(lactic-co-glycolic Acid) Biodegradable Microspheres: Release Kinetics and Stability Issues. J. of Microencap. **1998**, *15* (6), 699–713.
24. Putney, S.D.; Burke, P.A. Improving Protein Therapeutics with Sustained-Release Formulations. Nat. Biotechnol. **1998**, *16* (2), 153–157.
25. Sanders, L.M.; Kent, J.S.; McRae, G.I.; Vicery, B.H.; Tice, T.R.; Lewis, D.H. Controlled Release of a Luteinizing Hormone-releasing Hormone Analog from Poly(D,L-lactide-co-glycolide) Microspheres. J. Pharm. Sci. **1984**, *73* (9), 1294–1294.
26. Jacobi, G.H.; Wenderoth, U.K.; Ehrenthal, W.; von Wallenberg, H.; Spindler, H.W.; Hohenfellner, R. Endocrine and Clinical Evaluation of 107 Patients With Advanced Prostatic Carcinoma Under Long-term Pernasal Buserelin or Intramuscular Decapeptyl Depot Treatment. Am. J. Clin. Oncol. **1988**, *11* (Suppl.1), S36–S43.
27. Dlugi, A.M.; Miller, J.D.; Knittle, J. Lupron Depot (Leuprolide Acetate for Depot Suspension) in the Treatment of Endometriosis: A Randomized, Placebo-controlled, Double-blind Study. Lupron Study Group. Fertil. Steril. **1990**, *54* (3), 419–427.
28. Akaza, H.; Usami, M.; Koiso, K.; Kotake, T.; Aso, Y.; Niijima, T. Long-term Clinical Study on Luteinising Hormone-releasing Hormone Agonist Depot Formulation in the Treatment of Stage D Prostatic Cancer. The TAP-144-SR Study Group. Jpn. J. Clin. Oncol. **1992**, *22* (3), 177–184.
29. Neely, E.K.; Hintz, R.L.; Parker, B.; Bachrach, L.K.; Cohen, P.; Olney, R.; Wilson, D.M. Two-year Results of Treatment With Depot Leuprolide Acetate for Central Precocious Puberty. J. Pediatr. **1992**, *121* (4), 634–640.

30a. Hunter, S.J.; Shaw, J.A.M.; Lee, K.O.; Woods, P.J.; Atkinson, A.B.; Bevan, J.S. Comparison of Monthly Intramuscular Injections of Sandostatin LAR with Multiple Subcutaneous Injections of Octreotide in the Treatment of Acromegaly; Growth Hormone Secretion. Clin. Endocrinol.(Oxf.) **1998**, *50*, 245–251.

30b. Davies, P.H.; Stewart, S.E.; Lancranjan, L.; Sheppard, M.C.; Stewart, P.M. Long-term Therapy with Long-acting Octreotide (Sandostatin-LAR) for the Management of Acromegaly. Clin. Endocrinol.(Oxf.) **1998**, *48* (3), 311–316.

31. Rubin, J.; Ajani, J.; Schirmer, W.; Venook, A.P.; Bukowski, R.; Pommier, R.; Saltz, L.; Dandona, P.; Anthony, L. Octreotide Acetate Long-acting Formulation Versus Open-label Subcutaneous Octreotide Acetate in

Malignant Carcinoid Syndrome. J. Clin. Oncol. **1999**, *17* (2), 600–606.
32. Johnson, O.L.; Jaworowicz, W.; Cleland, J.L.; Bailey, L.; Charnis, M.; Duenas, E.; Wu, C.; Shepard, D.; Magil, S.; Last, T.; Jones, A.J.; Putney, S.D. The Stabilization and Encapsulation of Human Growth Hormone into Biodegradable Microspheres. Pharm. Res. **1997**, *14* (6), 730–735.
33. Berner, B.; Dinh, S. Fundamental Concepts in Controlled Release. *Treatise on Controlled Drug Delivery*; Kydonieus, A., Ed.; Marcel Dekker, Inc.: New York, 1992.
34. Heller, J. Fundamentals of Polymer Science. *Controlled Drug Delivery*; Robinson, J.R., Lee, V.H.L., Swarbrick, J., Eds.; From Series: Drugs and the Pharmaceutical Sciences, Chapter 3: Marcel Dekker, Inc.: New York, 1987; 29.
35. Bruck, S.D.; Mueller, E.P. Materials and Biological Aspects of Synthetic Polymers in Controlled Drug Release Systems: Problems and Challenges. Critical Reviews in Therapeutic Drug Carrier Systems **1988**, *5* (3), 171–187.
36. Cohen, S.; Yoshioka, T.; Lucarelli, M.; Hwang, L.H.; Langer, R. Controlled Delivery Systems for Proteins Based on Poly(Lactic/glycolic Acid) Microspheres. Pharm. Res. **1991**, *8* (6), 713–720.
37. Joshi, A.; Himmelstein, K.J. Dynamics of Controlled Release from Bioerodible Matrices. J. Control. Rel. **1991**, *15*, 95–104.
38. Lee, P.I. Diffusional Release of a Solute from a Polymeric Matrix — Approximate Analytical Solutions. J. Membr. Sci. **1980**, *7*, 255–275.
39. Hopfenberg, H.B. Controlled Release from Erodible Slabs, Cylinders, and Spheres. *Controlled Release Polymeric Formulations*; Paul, D.R., Harris, F.W., Gould, R.F., Eds.; American Chemical Society: Washington DC, 1976.
40. Kopecek, J.; Ulbrich, K. Biodegradation of Biomedical Polymers. Prog. Polym. Sci. **1983**, *9*, 1–58.
41. Gilding, D.K.; Reed, A.M. Biodegradable Polymers for Use in Surgery — Polyglycolic/Poly(Lactic Acid) Homo- and Copolymers: 1. Polymer **1979**, *20*, 1459–1464.
42. Li, S.M.; Garreau, H.; Vert, M. Structure –property Relationships in the Case of the Degradation of Massive Poly-(α-hydroxy Acids) in Aqueous Media, Part 1. Poly(DL-Lactic Acid). J. Mater. Sci. Mater. in Med. **1990**, *1*, 123–130.
43. Reed, A.M.; Gilding, D.K. Biodegradable Polymers for Use in Surgery — Polyglycolic/Poly(Lactic Acid) Homo- and Copolymers: 2. In Vitro Degradation. Polymer **1981**, *22*, 494–498.
44. Fukuzaki, H.; Yoshida, M.; Asano, M.; Kumakura, M. Synthesis of Copoly(D,L-Lactic Acid) With Relatively Low Molecular Weight and In Vitro Degradation. Eur. Polym. J. **1989**, *25* (10), 1019–1026.
45. Jain, R.; Shah, N.H.; Malick, A.W.; Rhodes, C.T. Controlled Drug Delivery by Biodegradable Poly(ester) Devices: Different Preparative Approaches. Drug Dev. and Ind. Pharm. **1998**, *24* (8), 703–727.
46. O'Hagan, D.T. Recent Advances in Vaccine Adjuvants for Systemic and Mucosal Administration. J. Pharm. Pharmacol. **1997**, *49*, 1–10.
47. Leong, K.W.; Brott, B.C.; Langer, R. Bioerodible Polyanhydrides as Drug-carrier Matrices. I: Characterization, Degradation and Release Characteristics. J. Biomed. Mat. Res. **1985**, *19*, 941–955.
48. Gopferich, A. Biodegradable Polymers: Polyanhydrides. In *The Encyclopedia of Controlled Release*; Mathiowitz, E., Ed.; Wiley: New York, 1999; 60–71.
49. Domb, A.J.; Nudelman, R. In Vivo and In Vitro Elimination of Aliphatic Polyanhydrides. Biomaterials **1995**, *16* (4), 319–323.
50. Tabata, Y.; Gutta, S.; Langer, R. Controlled Delivery Systems for Proteins Using Polyanhydride Microspheres. Pharm. Res. **1993**, *10* (4), 487–496.
51. Leong, K.W.; Kost, J.; Mathiowitz, E.; Langer, R. Polyanhydrides for Controlled Release of Bioactive Agents. Biomaterials **1986**, *7*, 364–371.
52. Laurencin, C.T.; Pierre-Jacques, H.M.; Langer, R. Toxicology and Biocompatibility Considerations in the Evaluation of Polymeric Materials for Biomedical Applications. **1990**, *10* (3), 549–570.
53. Leong, K.W.; D'Amore, P.; Marletta, M.; Langer, R. Bioerodible Polyanhydrides as Drug-Carrier Matrices. II: Biocompatibility And Chemical Reactivity. J. Biomed. Mat. Res. **1986**, *20*, 51–64.
54. Tamada, J.; Langer, R. The Development of Polyanhydrides for Drug Delivery Applications. J. Biomater. Sci., Polym. Ed. **1992**, *3* (4), 315–353.
55. Dang, W.; Daviau, T.; Brem, H. Morphological Characterization of Polyanhydride Biodegradable Implant Gliadel During In Vitro and In Vivo Erosion Using Scanning Electron Microscopy. Pharm. Res. **1996**, *13* (5), 683–691.
56. Heller, J. Controlled Drug Release from Poly(Ortho Esters) — A Surface Eroding Polymer. J. Control. Rel. **1985**, *2*, 167–177.
57. Heller, J. Development of Poly(Ortho Esters): A Historical Overview. Biomaterials **1990**, *11*, 659–665.
58. Heller, J. Poly(Ortho Esters). Adv. Polym. Sci. **1993**, *107*, 41–92.
59. Heller, J. Poly(Ortho Esters). *The Encyclopedia of Controlled Release*; Mathiowitz, E., Ed.; Wiley: New York, 1999; 852–874.
60. Heller, J.; Barr, J.; Ng, S.Y.; Shen, H-R.; Schwach-Abdellaoui, K.; Emmahl, S.; Rothen-Weinhold, A.; Gurny, R. Poly(Ortho Esters)- Their Development and Some Recent Applications. Eur. J. Pharm. Biopharm. **2000**, *50* (1), 122–128.
61. Rothen-Weinhold, A.; Heller, J.; Barr, J.; Gurny, R. Poly(Ortho Esters) Implants for the Sustained Delivery of a Protein: Factors Influencing the Release Behavior of BSA In Vitro. Proc Intl. Symp. Control. Rel. Bioact. Mater. **2000**, *27*, 8004.
62. Laurencin, C.T.; Koh, H.J.; Neenan, T.X.; Allcock, H.R.; Langer, R. Controlled Release Using a New Bioerodible Polyphosphazene Matrix System. J. Biomed. Mat. Res. **1987**, *21*, 1231–1246.
63. Allcock, H.R.; Pucher, S.R.; Scopelianos, A.G. Poly [(Amino Acid Ester)phosphazenes] as Substrates for the Controlled Release of Small Molecules. Biomaterials **1994**, *15* (8), 563–569.
64. Payne, L.G.; Andrianov, A.K. Protein Release from Polyphosphazene Matrices. Adv. Drug Deliv. Rev. **1998**, *31* (3), 185–196.
65. Caliceti, P.; Lora, S.; Marsilio, F.; Veronese, F.M. Preparation and Characterization of Polyphosphazene-based Controlled Release Systems for Naproxen. Farmaco **1995**, *50* (12), 867–874.

66. Veronese, F.M.; Marsilio, F.; Caliceti, P.; De Filippis, P.; Giunchedi, P.; Lora, S. Polyorganophosphazene Microspheres for Drug Release: Polymer Synthesis, Microsphere Preparation, In Vitro and In Vivo Naproxen Release. J. Control. Rel. **1998**, *52* (3), 227–237.
67. Ibim, S.M.; el-Amin, S.F.; Goad, M.E.; Ambrosio, A.M.; Allcock, H.R.; Laurencin, C.T. In Vitro Release of Colchicine Using Poly(Phosphazenes): The Development of Delivery Systems for Musculoskeletal Use. Pharm. Dev. Technol. **1998**, *3* (1), 55–62.
68. Veronese, F.M.; Marsilio, F.; Lora, S.; Caliceti, P.; Passi, P.; Orsolini, P. Polyphosphazene Membranes and Microspheres in Periodontal Diseases and Implant Surgery. Biomaterials **1999**, *20* (1), 91–98.
69. Richards, M.; Dahivat, B.I.; Arm, D.M.; Brown, P.R.; Leong, K.W. Evaluation of Polyphosphates and Polyphosphonates as Degradable Biomaterials. J. Biomed. Mat. Res. **1991**, *25*, 1151–1167.
70. Saltzman, W.M.; Parsons-Wingerter, P.; Leong, K.W.; Lin, S. Fibroblast and Hepatocyte Behavior on Synthetic Polymer Surfaces. J. Biomed. Mat. Res. **1991**, *25*, 741–759.
71. Mao, H-Q.; Kadivala, I.; Leong, K.W.; Zhao, Z.; Dang, W. Biodegradable Polymers: Poly(Phosphoester)s. *The Encyclopedia of Controlled Release*; Mathiowitz, E., Ed.; Wiley: New York, 1999; 45–60.
72. Harper, E.; Dang, W.; Lapidus, R.G.; Garver, R.I. Enhanced Efficacy of a Novel Controlled Release Paclitaxel Formulation (PACLIMER® Delivery System) for Local-regional Therapy of Lung Cancer Tumor Nodules in Mice. Clin. Cancer Res. **1999**, *5*, 4242–4248.
73. Wee, S.; Gombotz, W.R. Protein Release from Alginate Matrices. Adv. Drug Deliv. Rev. **1998**, *31* (3), 267–285.
74. Cadee, J.A.; van Luyn, M.J.; Brouwer, L.A.; Plantinga, J.A.; van Wachem, P.B.; deGroot, C.J.; den Otter, W.; Hennink, W.E. In Vivo Biocompatibility of Dextran-based Hydrogels. J. Biomed. Mater. Res. **2000**, *50* (3), 397–404.
75. Rao, K.P. Recent Developments of Collagen-based Materials for Medical Applications and Drug Delivery Systems. J. Biomater. Sci., Polym. Ed. **1995**, *7* (7), 623–645.
76. Ikada, Y.; Tabata, Y. Protein Release from Gelatin Matrices. Adv. Drug Deliv. Rev. **1998**, *31* (3), 287–301.
77. D'Urso, E.M.; Jean-Francois, J.; Doillon, C.J.; Fortier, G. Poly(Ethylene Glycol)-Serum Albumin Hydrogel as Matrix for Enzyme Immobilization: Biomedical Applications. Artif. Cells Blood Substit. Immobil. Biotechnol. **1995**, *23* (5), 587–595.
78. Sawhney, A.S.; Pathak, C.P.; van Rensburg, J.J.; Dunn, R.C.; Hubbell, J.A. Optimization of Photopolymerized Bioerodible Hydrogel Properties for Adhesion Prevention. J. Biomed. Mat. Res. **1994**, *28*, 831–838.
79. Markland, P.; Zhang, Y.; Amidon, G.L.; Yang, V.C. A pH- and Ionic Strength-responsive Polypeptide Hydrogel: Synthesis, Characterization, and Preliminary Protein Release Studies. J. Biomed. Mat. Res. **1999**, *47* (4), 595–602.
80. Kamath, K.R.; Park, K. Biodegradable Hydrogels in Drug Delivery. Adv. Drug Deliv. Rev. **1993**, *11*, 59–84.
81. Kim, B-S.; Mooney, D.J. Development of Biocompatible Synthetic Extracellular Matrices for Tissue Engineering. Tibtech **1998**, *16*, 224–230.
82. Wald, H.L.; Sarakinos, G.; Lyman, M.D.; Mikos, A.G.; Vacanti, J.P.; Langer, R. Cell Seeding in Porous Transplantation Devices. Biomaterials **1993**, *14* (4), 270–278.
83. Murphy, W.L.; Mooney, D.J. Controlled Delivery of Inductive Proteins, Plasmid DNA, and Cells from Tissue Engineering Matrices. J. Periodont. Res. **1999**, *34*, 413–419.
84. Juang, J-H.; Bonner-Weir, S.; Vacanti, J.P.; Weir, G.C. Outcome of Subcutaneous Islet Transplantation Improved by a Polymer Device. Transplantation Proceedings **1995**, *27* (6), 3215–3217.
85. Cohen, S.; Bano, M.C.; Cima, L.G.; Allcock, H.R.; Vacanti, J.P.; Vacanti, C.A.; Langer, R. Design of Synthetic Polymeric Structures for Cell Transplantation and Tissue Engineering. Clin. Mater. **1993**, *13* (1–4), 3–10.
86. Lim, F.; Sun, A.M. Microencapsulated Islets As Bioartificial Endocrine Pancreas. Science **1980**, *210* (21), 908–910.
87. Laurencin, C.T.; El-Amin, S.F.; Ibim, S.E.; Willoughby, D.A.; Attawia, M.; Allcock, H.R.; Ambrosio, A.A. A Highly Porous 3-Dimensional Polyphosphazene Polymer Matrix for Skeletal Tissue Regeneration. J. Biomed. Mat. Res. **1996**, *30*, 133–138.
88. Meikle, M.C.; Papaioannou, S.; Ratledge, T.J.; Speight, P.M.; Watt-Smith, S.R.; Hill, P.A.; Reynolds, J.J. Effect of Poly D-lactide-co-glycolide Implants and Xenogeneic Bone Matrix-derived Growth Factors on Calvarial Bone Repair in the Rabbit. Biomaterials **1994**, *15* (7), 513–521.
89. Peter, S.J.; Miller, M.J.; Yaszemski, M.J.; Mikos, A.G. Polymer Concepts in Tissue Engineering. J. Biomed. Mat. Res. **1998**, *43*, 422–427.
90. Kim, S.S.; Vacanti, J.P. The Current Status of Tissue Engineering As Potential Therapy. Semin. Pediatr. Surg. **1999**, *8* (3), 119–123.